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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,651	MOLLOY ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-67,69-85,87-95 and 97-106* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-56,60-65,67,69-73,79-85,87-95 and 97-106* is/are rejected.

7)☒ Claim(s) *57-59,66 and 74-78* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Receipt is acknowledged of an amendment, filed 6/23/2004, in which a new copy of the sequence listing, CRF, attorney's statements concerning the substitute sequence listing and an amendment to the specification were submitted. The substitute sequence listing has been entered into the file and the case is in sequence compliance. The amendment to the specification provides a sequence identifier (i.e. SEQ ID NO: 2) that corresponds to the sequence incorporated by reference to O'Keefe et al at page 5 of the instant specification.

Receipt is further acknowledged of an initial response, filed 3/18/2004 in which claims were amended (54, 65-67, 69-72, 85, 87-89, 95 & 97-99) and in which claims were cancelled (claims 68, 86 & 96). Receipt is also acknowledged of a Declaration submitted by one of the inventors, Peter Laurence Molloy, under 35 U.S.C. § 1.132. The declaration and applicants' response have been considered in full and have been found persuasive with regard to treatment of prostate cancer with a vector comprising the recited enhancer element operatively linked to a polynucleotide sequence encoding an enzyme that converts a prodrug to a toxic drug. Other *in vivo* embodiments remain unenabled for reasons of record and which are discussed below in response to applicants' arguments.

Any rejection of record in the office action mailed 11/19/2003 not addressed herein is withdrawn. Claims 54-67, 69-85, 87-95 and 97-106 are pending and under consideration in the instant office action. This action is <u>not</u> final as there are new rejections made herein that were not necessitated by applicants' amendment of the claims in the response filed 3/18/2004.

Specification

In the office action mailed 11/19/2003, the examiner objected to an attempt to incorporate subject matter into this application by reference to O'Keefe et al as being improper because the nucleic acid sequence represented by AF007544 is essential matter. In response, applicants have filed on 3/18/2004 & 6/23/2004 amendments to incorporate into the sequence listing the specific nucleic acid sequence represented by Accession No. AF007544. In addition, these responses amend the specification to provide the appropriate sequence identifier for the incorporated sequence (i.e. SEQ ID NO: 2 corresponding to AF007544). However, the accompanying statement from applicants' representative stating that the amendatory material consists of the same material incorporated by reference in the instant application refers to the wrong sequence identifier (i.e. SEQ ID NO: 1; see the response filed 3/18/2004, page 11). It is requested that applicants' representative correct the record by explicitly indicating that the sequence described by SEQ ID NO: 2 is what is incorporated by reference. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 85, 87-95, 97-106 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) *in vitro* embodiments directed to expression of a desired polypeptide sequence when the polynucleotide sequence is operatively linked to the recited PSMA enhancer element and promoter, and (ii) methods of treating prostate cancer wherein the vector used comprises a recombinant expression cassette comprising a polynucleotide sequence encoding an enzyme that converts a prodrug to a toxic drug operatively linked to both an enhancer element obtained from intron 3 of the PSM gene and a promoter element, does not reasonably provide enablement for any other *in vivo* embodiments wherein the claimed regulatory elements are used to direct expression of a given heterologous sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This is a new rejection.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The invention is extraordinarily complex, encompassing the use of novel transcriptional regulatory elements (i.e. enhancer elements obtained from the 3rd intron of the human prostate specific membrane antigen gene) to drive expression of a therapeutic nucleic acid sequence in a given host organism such that efficacious treatment is achieved. The only disclosed utility for *in vivo* embodiments of the claimed invention for which the

specification provides any significant guidance at all is for the therapeutic treatment of a disease or condition in a human (e.g. prostate cancer). Thus, the rejected claims read on *in vivo* gene therapy.

Breadth of the claims: The breadth of the claims greatly exacerbates the complexity of the invention. The broadest claims encompass any disease or condition (e.g. any cancer). The claims encompass the use of any gene sequence or antisense sequence to achieve a therapeutic effect when operatively linked to the prostate-specific enhancer element of the invention.

Guidance of the specification/The existence of working examples: The specification teaches the isolation and characterization of an ~2.5 kb enhancer region obtained from the 3rd intron of the PMSA gene (e.g. Examples 1-3 of the instant specification). The working examples teach *in vitro* experiments that demonstrate multiple constructs obtained from the 3rd intron of the PMSA gene can enhance the tissue-specific expression of operatively-linked nucleic acid sequences when linked to different promoter elements (e.g. probasin promoter, prostate specific antigen gene promoter (i.e. the PSA promoter), herpes simplex virus thymidine kinase promoter (i.e. the TK promoter), etc.; e.g. Example 7, Figure 9a). In general, the tissue specificity observed for the different enhancer elements mirrors the expression data for the PSMA gene in different cell types, with by far the greatest level of enhancement activity observed in prostate cell types such as LN3 or PC3 (e.g. Examples 4-7 & 10, Figure 7). This strong tissue-specificity for prostate cell types was maintained when the enhancer elements were presented as part of an ovine atadenoviral backbone (e.g. Example 12, Figure 12). Although the specification speculates that the level of expression seen in the kidney cell line tested (i.e. HEK293 cells) might be biologically meaningful since PSMA is expressed at low levels in proximal kidney tubules, the

level of enhancement of expression is low relative to prostate cell lines (e.g. Figures 9a & 9b). A single working example is provided concerning enhancement of expression activity in human umbilical artery cells (HUAECs) or vein cells (HUVECs) since PSMA is known to be expressed in the neovasculature of several tumor types, but not in normal vasculature (e.g. Example 13). While it is stated that an enhancer element of the invention did result in some degree of neovasculature-specific enhancement of operatively-linked reporter sequences in the HUAEC and HUVEC cells, the level of enhancement is not indicated.

While the specification asserts other *in vivo* utilities for the claimed methods of expressing a gene operatively linked to the enhancer elements of the invention (e.g. providing a target for the development of agents that may interfere with gene expression in the target cell types-page 4, last paragraph), no significant guidance is provided for any of these asserted utilities. No working examples are provided, for example, where a given "therapeutic gene" is operatively linked to an enhancer element of the invention and efficacious expression is observed in an animal model for a given disease (e.g. a given type of cancer).

State of the art/Predictability of the art: The prior art appears to be silent with regard to the use of the specific enhancer elements taught in the instant specification. Thus, the prior art does not offset the deficiencies of the instant specification with regard to enabling the full, broadly claimed scope of the invention.

In general, gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See Orkin et al (U) which states (page 1):

2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal

claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host.

The consensus scientific opinion is that gene therapy was and still is highly unpredictable as evidenced by Orkin et al. The teachings of Verma et al (V), two years after the Orkin et al publication, reaffirm the teachings of Orkin et al that, even after the two years, there is no evidence of how to use gene therapy to predictably to treat any disease. Verma et al teach "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story." (Page 239, column 1). This reference teaches the considerable hurdles that must be overcome, including making sure that delivery of the gene gets to the right cells and getting enough of the gene delivered (page 239). This reference teaches that "The Achilles heel of gene therapy is gene delivery....Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression. Most of these approaches suffer from poor efficiency of delivery and transient expression of the gene." (page 236, column 3). Palù et al (J. Biotechnol. (1999) 68: 1-13) teaches that despite hundreds of clinical trials underway, no successful outcome has been achieved (Palù et al, p. 1, Abstract). The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology

(2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient (e.g. see p. 33, Abstract and col. 1, 1st and 2nd paragraphs).

Although the references cited above indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. As recently as April of 1998 French Anderson (W) reviewed the status of the field of gene therapy and concluded that "Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease." (page 25, column 1). More recently, the most advanced clinical trial for the gene therapy treatment of severe combined immunodeficiency disease (SCID), the only disease for which has purportedly been "cured" by gene therapy, has been halted due to the development of cancer in two of the subjects. In both cases the retrovirus used to deliver the corrective gene to the patient inserted itself into a stretch of a gene associated with childhood leukemia (Nature, February 2003, Vol. 421, page 678, "Cancer fears cast doubts on future of gene therapy").

The amount of experimentation necessary: Given the factors outlined above, especially with regard to the high state of the art required to practice gene therapy, and the unpredictability of the art with regard to gene therapy in general, it would have required undue, unpredictable experimentation to practice the claimed invention in the full, broadly claimed scope encompassed by the rejected claims.

Response to Arguments

Applicant's arguments and evidentiary declaration filed 3/18/2004 in response to similar grounds of rejection made in the previous office action have been fully considered but they are

not completely persuasive. The response essentially argues: 1) claims 85-94 do not recite specific steps concerning the treatment of disease and do not require that a therapeutic effect is obtained, 2) the specification exemplifies embodiments where operatively linked genes are expressed in cells in culture, 3) the specification does in fact assert additional utilities for the recited methods other than just treatment (e.g. page 4, last paragraph), 4) the specification provides several examples of the specificity of enhancement of expression in a variety of cell types and at different levels, 5) the declaration by Mr. Molloy provides experimental evidence of regulated expression of operatively-linked genes in mouse models for prostate cancer, 6) the experiments described by the declaration are direct evidence that the methods of claims 85-94, which require expression of a coding sequence operably linked to the enhancer element are enabled, 7) the declaration further provides evidence that expression of the purine nucleoside phosphorylase (PNP) gene as provided by the enhancer elements of the invention is therapeutic in effect.

The declaration provided by Mr. Molloy has been considered in full and is persuasive with regard to treatment of prostate cancer in methods where the enhancer element of the invention is used to regulate expression of an operatively linked nucleic acid sequence encoding an enzyme that can convert a prodrug to a toxic drug *in vivo* (e.g. see page 7, lines 27-32 of the instant specification). The animal model systems used in the experiments described in the declaration by Mr. Molloy are apparently art-accepted models for prostate cancers and the data is convincing with regard to reduction in tumor size and increased life expectancy for mice receiving treatment with the oatadenovirus vector encoding the PNP gene under control of one of the enhancer elements of the invention. Further, it is known in the art that the amount of

enzymes such as PNP that need be expressed in a given cell type for their effects to be toxic is not great and need not be fine-tuned to a particular level of expression in order for the host cell to be killed. Therefore, it is reasonable in view of the evidence provided by the declaration to consider the instant specification enabling for *in vivo* embodiments directed to the treatment of prostate cancer with expression cassettes comprising an enhancer/promoter element of the invention operatively linked to a sequence encoding such enzymes.

Given the difference in expression levels observed in the instant specification for the claimed nucleic acids in cell types other than prostate cells (e.g. neovascular cells, etc.), the absence of any data with regard to animal models for other types of cancers involving other cell types (e.g. breast cancer), and the lack of significant guidance with regard to other types of cancer (e.g. which animal model system to use, which genes to express, etc.), it would take undue unpredictable experimentation to use the recited methods in their full, broad scope as currently claimed.

With regard to claims 85-94, it is acknowledged that the rejected claims do not expressly recite any therapeutic effect in treatment of any particular disease. However, the only significant guidance provided by the specification for *in vivo* embodiments of the broadly claimed methods is for treatment of disease (e.g. cancer). While the specification asserts that other utilities are possible for using the claimed enhancer elements *in vivo*, no significant, specific guidance is given towards these ends. For example, the specification asserts that the claimed enhancer elements might be used to develop transgenic animal models for prostate disease but does not provide any working example or instruction to achieve this goal without undue, unpredictable

experimentation. Therefore, the scope of enablement rejection limiting claims 85-94 to the embodiments recited above is maintained.

Claims 64 and 72-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the previous office action that are repeated below.**

The rejected claims are all broadly drawn to "regulatory elements" derived from the 3rd intron of the PMSA gene described by O'Keefe et al. Many of the pending claims recite that the regulatory element is an enhancer. Thus, the claims reasonably encompass other types of "regulatory elements" such as repressor sequences, RNA destabilization/stabilization sequences, etc. The instant specification, however, describes the instant invention solely in the context of enhancer elements obtained from intron 3 of the PMSA gene. Therefore, there is no basis for the skilled artisan to envision those embodiments that are not enhancer elements. The skilled artisan would have concluded, for this reason that applicants were not in possession of the broadly claimed compositions and methods.

Response to Arguments

Applicant's arguments filed 3/18/2004 in response to similar grounds of rejection made in the previous office action have been fully considered but they are not completely persuasive. The response essentially argues that the amendment of the claims to recite an "enhancer element" rather than "regulatory element" has obviated the outstanding grounds of rejection. This

assertion is not accurate for the rejected claims as the limitation "regulatory element" is still present in these claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 60-63, 69-71, 79-84, 87-89 & 97-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 60 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the regulatory element" in claim 54, upon which claim 60 is dependent.

Claims 61-63, 69-71, 79-84, 87-89 & 97-99 each recite a limitation regarding hybridization under "high stringency". This term does not appear to be described in the specification as meaning a particular set of hybridization conditions and is open to interpretation by the skilled artisan. **This rejection is maintained for reasons of record in the previous office action.**

Response to Arguments

Applicant's arguments filed 3/18/2004 have been fully considered but they are not persuasive. The response essentially argues that the specification provides a definition for the term "high stringency conditions" at pages 8-9 of the instant specification that is "the standard definition" and which would be recognized by those of skill in the art. This argument is not persuasive in that it is factually inaccurate and unsupported by the instant specification or prior art. The definition provided in the instant specification is not explicitly limited to any single set

of conditions and merely provides alternative examples of what might be considered highly stringent conditions for hybridization. As indicated by the examiner, the metes and bounds of the term are still open to interpretation, even in spite of the examples provided in the instant specification, and are not definite. If applicants wish to use the term "high stringency" in the instant claims it will be necessary to further amend the claim to recite one of the specific sets of conditions recited in the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejected claims are directed to recombinant polynucleotides comprising at least one enhancer element obtained from intron 3 of the PSM (prostate specific membrane) gene and a sequence encoding a heterologous polypeptide. There is no explicit linkage in the claims linking the enhancer element and the heterologous nucleic acid sequence such that the claims can be interpreted to read on any cloning vector comprising intron 3 of the PSM gene so long as the vector encodes a heterologous protein (e.g. an antibiotic resistance marker).

Claims 54-56, 60-63, 65, 67, 69-71 & 79-83 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Keefe et al (Biochimica et Biophysica Acta, Vol. 1443, pages 113-127, 1998; see the entire reference). **This is a new rejection. It would be remedial to amend the claim**

language to clearly indicate that the enhancer element is operatively linked to the nucleic acid sequence encoding a heterologous gene.

The O'Keefe et al reference teaches the mapping, genomic organization and promoter analysis for the human prostate-specific membrane antigen gene (e.g. Abstract). Bacteriophage P1 vectors were used to generate a library of clones from human tissue that were screened using PCR-based methods for the 5' and 3' ends of the human cDNA for PSMA. Intron 3 is specifically disclosed in Table 1. Clone P1-683 is disclosed as comprising the intron 3 sequence (e.g. Figure 1). One of skill in the art would necessarily expect the P1 vectors taught by O'Keefe to express at least one gene encoding a polypeptide other than PMSA.

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Conclusion

Claims 54-67, 69-85, 87-95 and 97-106 are pending and under consideration in the instant office action. Claims 54-56, 60-65, 67, 69-73, 79-85, 87-95 and 97-106 are rejected. Claims 57-59, 66 and 74-78 are objected to as being dependent on a rejection claim, but would be otherwise allowable if rewritten as independent claims comprising each of the limitations of the claims upon which they are currently dependent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
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GERRY LEFFERS
PRIMARY EXAMINER

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